Complete Summary

GUIDELINE TITLE

Lipid management in adults.

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Lipid management in adults. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2006 Jun. 76 p. [128 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Lipid management in adults. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2005 Jun. 82 p.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

On March 2, 2005, the U.S. Food and Drug Administration (FDA) issued a public health advisory describing revisions to the WARNINGS, DOSAGE AND ADMINISTRATION, CLINICAL PHARMACOLOGY, and PRECAUTIONS sections of the labeling for the drug Crestor (rosuvastatin calcium). The revisions include results from a Phase 4 pharmacokinetic study in Asian-Americans and highlight important information on the safe use of Crestor to reduce the risk for serious muscle toxicity (myopathy/rhabdomyolysis), especially at the highest approved dose of 40 mg. At this time, the FDA is also making statements about the muscle and kidney safety of Crestor based on extensive review of available information. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **
SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
CONTRAINDICATIONS

QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Dyslipidemias, including:

- High low-density lipoprotein (LDL)-cholesterol
- High triglycerides
- Isolated low high-density lipoprotein (HDL)-cholesterol

GUIDELINE CATEGORY

Evaluation
Management
Prevention
Risk Assessment
Treatment

CLINICAL SPECIALTY

Cardiology
Endocrinology
Family Practice
Internal Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Dietitians
Health Care Providers
Health Plans
Hospitals
Managed Care Organizations
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To increase the percentage of patients whose 10-year risk is greater than 20% or with known coronary heart disease (CHD) or CHD equivalent who achieved low-density lipoprotein (LDL) goals

- To improve the percentage of patients without known CHD or CHD equivalent with lipid disorders who meet their treatment goal
- To increase adherence with adjunctive treatment of patients with CHD or CHD equivalent through education (see floating box 3-6 on algorithm page in the original guideline document)
- To improve the percentage of patients on lipid lowering medication who receive regular follow-up care for lipid disorder
- To increase the percent of patients on lipid lowering therapy who remain on therapy

TARGET POPULATION

Adults, age 20 and older, who are dyslipidemic

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation/Risk Assessment

1. Measurement of triglycerides, total cholesterol, high-density lipoprotein (HDL)-cholesterol; calculation of low-density lipoprotein (LDL)-cholesterol
2. Calculation of 10-year risk for coronary heart disease (CHD) or adding up cardiac risk factors
3. Evaluation for secondary causes of abnormal lipid levels, such as screening for diabetes and hypothyroidism, and consideration of other potential secondary causes in patients with elevated triglycerides
4. Establishment of lipid goals based on risk level

Management/Treatment/Prevention

1. Patient education on lifestyle modification, including:
    - Diet
    - Physical activity
    - Weight management
    - Aspirin
    - Evaluation of alcohol consumption
    - Fish oil (EPA-DHA)
    - Smoking cessation
    - Nutritional supplements containing B-sitosterol or sitostanol ester
2. Pharmacologic management
    - Statin therapy
    - Bile acid sequestrants
    - Niacin
    - Fibric acids
    - Selective cholesterol absorption inhibitor
    - Combination therapy
    - Ethyl esters of omega-3 fatty acids, fish oil
3. Follow-up, including:
    - Assessment of adherence to therapy
    - Laboratory monitoring
    - Referral as indicated

MAJOR OUTCOMES CONSIDERED

- Risk of cardiovascular and cerebrovascular fatal and nonfatal events
- Lipoprotein measures, including triglyceride concentrations, high-density lipoprotein (HDL)-cholesterol, total cholesterol, and low-density lipoprotein (LDL)-cholesterol
- Safety, efficacy, cost, and side effects of drugs

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system presented below, and are designated as positive, negative, or neutral to reflect the study quality.

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Study Quality Designations:

The quality of the primary research reports and systematic reviews are designated in the following ways on the conclusion grading worksheets:

Positive: indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis.

Negative: indicates that these issues (inclusion/exclusion, bias, generalizability, and data collection and analysis) have not been adequately addressed.

Neutral: indicates that the report or review is neither exceptionally strong nor exceptionally weak.

Not Applicable: indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series

- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A published cost analysis was reviewed.

METHOD OF GUIDELINE VALIDATION

Clinical Validation-Pilot Testing
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Institute Partners: System-Wide Review

The guideline draft, discussion, and measurement specification documents undergo thorough review. Written comments are solicited from clinical, measurement, and management experts from within the member medical groups during an eight-week period of "Critical Review."

Each of the Institute's participating medical groups determines its own process for distributing the guideline and obtaining feedback. Clinicians are asked to suggest modifications based on their understanding of the clinical literature coupled with their clinical expertise. Representatives from all departments involved in implementation and measurement review the guideline to determine its operational impact. Measurement specifications for selected measures are developed by the Institute for Clinical Systems Improvement (ICSI) in collaboration with participating medical groups following general implementation of the guideline. The specifications suggest approaches to operationalizing the measure.

Guideline Work Group: Second Draft

Following the completion of the "Critical Review" period, the guideline work group meets 1 to 2 times to review the input received. The original guideline is revised as necessary, and a written response is prepared to address each of the suggestions received from medical groups. Two members of the Cardiovascular Steering Committee carefully review the Critical Review input, the work group responses, and the revised draft of the guideline. They report to the entire committee their assessment of two questions: (1) Have the concerns of the medical groups been adequately addressed? (2) Are the medical groups willing and able to implement the guideline? The committee then either approves the guideline for pilot testing as submitted or negotiates changes with the work group representative present at the meeting.

Pilot Test

Medical groups introduce the guideline at pilot sites, providing training to the clinical staff and incorporating it into the organization's scheduling, computer, and other practice systems. Evaluation and assessment occurs throughout the pilot test phase, which usually lasts for three months. Comments and suggestions are solicited in the same manner as used during the "Critical Review" phase.

The guideline work group meets to review the pilot sites' experiences and makes the necessary revisions to the guideline, and the Cardiovascular Steering Committee reviews the revised guideline and approves it for implementation.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC) and the Institute for Clinical Systems Improvement (ICSI): In addition to updating their clinical guidance, ICSI has developed a new format for all guidelines. Key additions and changes include: combination of the annotation and discussion section; the addition of "Key Points" at the beginning of most annotations; the

inclusion of references supporting the recommendations; and a complete list of references in the Supporting Evidence section of the guideline. For a description of what has changed since the previous version of this guidance, refer to "Summary of Changes -- June 2006."

The recommendations for lipid management in adults are presented in the form of an algorithm with 16 components, accompanied by detailed annotations. An algorithm is provided for Lipid Management in Adults; clinical highlights and selected annotations (numbered to correspond with the algorithm) follow.

Class of evidence (A-D, M, R, X) and conclusion grade (I-III, Not Assignable) definitions are repeated at the end of the "Major Recommendations" field.

Clinical Highlights and Recommendations

- Initiate a statin in patients who have a history of coronary heart disease (CHD) or CHD equivalent. (Annotation #8)
- There is no upper age cutoff for management of lipids. (Annotations #3-6)
- Establish lipid goals based on risk level. (Annotation #9)
- Instruct patients on healthy lifestyle and adjunctive measures. (Annotations #3-6)
- Patient adherence with recommended therapy should be reinforced during scheduled follow-up. (Annotation #13)
- Folic acid and vitamin B are not recommended for treatment of hyperhomocysteinemia or prevention of coronary artery disease (CAD). (Annotations #3-6)
- Low-density lipoprotein (LDL) goal less than 70 is recommended for patient with established CAD, noncardiac artherosclerosis or coronary artery disease equivalent (i.e., diabetes mellitus). (Annotation #9)

Lipid Management in Adults Algorithm Annotations

1. Patient Has Dyslipidemia or is at High Risk for Coronary Heart Disease (CHD)

   Secondary causes of abnormal lipid levels should be considered and treated when appropriate. Diet and exercise are the cornerstone of treatment for asymptomatic patients with dyslipidemia. Patients with an elevated LDL-cholesterol level should begin the American Heart Association (AHA) Step I diet and an individualized program of regular aerobic exercise. A diet low in fat, especially saturated fat, and high in soluble fiber is recommended. Patients who are overweight should be advised to reduce their calorie intake to achieve weight loss. Patients should follow the diet and exercise program for a reasonable amount of time to determine whether their LDL-cholesterol level is lowered to the target range. For many asymptomatic patients, a diet and exercise program is sufficient.

   Patients with a history of non-coronary atherosclerosis (including carotid occlusive vascular disease, abdominal aortic aneurysm, or peripheral vascular disease) or who have diabetes are at high-risk for CHD and are considered CHD equivalent.

Evidence supporting this recommendation is of class: A

2. Calculate 10-Year Risk for CHD or Add Up Cardiac Risk Factors

The National Cholesterol Education Program Adult Treatment Panel III (ATP III) defines high risk as a net of two or more (CHD) risk factors, which leads to more vigorous intervention. Identified risk factors are:

- Age 45 years or older for men; age 55 years or older, or premature menopause without hormone replacement therapy, for women. CHD rates are higher in the elderly than in the young, and in men than in women of the same age.
- A family history of premature CHD, defined as definite myocardial infarction (MI) or sudden death before age 55 in the father or a male primary relative, or before age 65 in the mother or a female primary relative
- Currently smoking
- Hypertension, defined as blood pressure greater than 140/90 mm Hg (confirmed by measurement on several occasions) or current use of any antihypertensive medication
- Low high-density lipoprotein (HDL)-cholesterol level (less than 40 mg/dL)
- Nontraditional risk factors (C-reactive protein [CRP] and total homocysteine) have been shown to have some predictive values in screening vascular disease. The value of screening for these risk factors is not yet known.

See Appendix A in the original guideline document, "Lipid Management in Adults -- Risk Calculator".

Obesity and physical inactivity are not listed as risk factors, but should be considered as targets for intervention. Obesity operates through other risk factors (hypertension, hyperlipidemia, decreased HDL-cholesterol, and diabetes mellitus).

If HDL-cholesterol is 60 mg/dL or higher, one risk factor may be subtracted, because high HDL-cholesterol levels decrease CHD risk. (For example, if a patient has three risk factors but his or her HDL-cholesterol level is 60 mg/dL or higher, one risk factor is subtracted, leaving a total of two risk factors.)

Please refer to the table below, "Management" (Appendix B in the original guideline document).

Table: Management

Type of Dyslipidemia	Lipid Subfractions	Primary Therapy	Secondary Therapy
High LDL-Cholesterol and Triglycerides	LDL: elevated HDL: $\geq$40 Triglycerides: >200	• Weight loss • Physical activity • Discontinue	Statin Niacin* Fish oil (EPA-DHA)

Type of Dyslipidemia	Lipid Subfractions	Primary Therapy	Secondary Therapy
	LDL: elevated HDL: <40 Triglycerides: >200	smoking • No alcohol • Improve diabetes mellitus control • Therapeutic lifestyle change (TLC)	Statin Fibric acids Niacin* Fish oil (EPA-DHA) Ezetimibe
High LDL-Cholesterol	LDL: elevated HDL: ≥40	• Weight loss • Physical activity • TLC • Discontinue smoking	Statin Fibric acids Niacin* Ezetimibe Bile Acid Sequestrant
	LDL: elevated HDL: <40		Statin Fibric acids Niacin* Bile Acid Sequestrant Ezetimibe
Isolated Low HDL-Cholesterol	HDL: <40 LDL is normal	• Physical activity • Discontinue smoking	(Drug recommendations for treatment remain controversial except in CHD.) Fibric acids** Statin Niacin*
High Triglycerides		• Weight loss • Discontinue smoking • No alcohol • Improved diabetes mellitus control • TLC • Physical activity	Fibric acids Niacin* Fish oil (EPA-DHA)

Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; CHD, coronary heart disease; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid

*Niacin can elevate glucose in patients with diabetes. Review the drug education sheet (provided in the original guideline document) with the patient when initiating niacin therapy.

**Although not U.S. Food and Drug Administration (FDA)-labeled, use of gemfibrozil is supported by the Department of Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) study.

If considering combination therapy or alternative agents, suggest lipid clinic consultation.

Evidence supporting these recommendations is of classes: B, C, D, R

Please refer to Annotation Appendix C in the original guideline document, "Identified Secondary Causes and Conditions Associated with Hyperlipidemia," for more information on secondary causes and conditions associated with hyperlipidemia.

3-6. Lifestyle Modification/Drug Therapy/Adjunctive Measures

Lifestyle modifications include diet, aerobic exercise, weight management, aspirin, evaluation of alcohol consumption, fish oil (EPA-DHA), smoking cessation, and nutritional supplement containing sitostanol ester, a saturated derivative of a plant seed. To avoid unintended toxic effects from vitamins, patients should be cautioned not to exceed recommended doses.

Vitamin E supplements should not be used. Studies have shown no benefit in preventing clinical outcomes and smaller studies suggest a blunting of the benefit from antidyslipidemic medications on HDL cholesterol (HDL-C) and angiographic progression of vascular disease.

In Annotation boxes #3-5 in the original guideline document, the LDL threshold for drug therapy is consistent with ATP-III. However, in particular cases, drug therapy may be considered at LDL thresholds 30 mg/dL lower than noted in Annotation boxes #3-5.

The decision to begin drug therapy must be based on a clinical discussion with the patient in which the evidence-based outcome data, possible side effects, and cost are weighed.

Please refer to the table above, "Management," (Annotation Appendix B in the original guideline document) and Annotation Appendix D, "Drug Companion Document" in the original guideline document for additional information.

Patients with risk factors for coronary heart disease but no history of disease who receive lipid lowering therapy are likely to experience a decreased risk of coronary heart disease. [Conclusion Grade I: See Conclusion Grading Worksheet A - Annotation #3-6 (Risk Factors and Lipid Lowering Therapy) in the original guideline document.]

Patients with a history of coronary disease (including unstable angina and acute myocardial infarction) often benefit from treatment with a statin. Studies have consistently shown a decrease in risk of death from coronary heart disease. [Conclusion Grade I: See Conclusion Grading Worksheet B - Annotations #3-6 (History of CHD) in the original guideline document.]

Metabolic Syndrome

Specific recommendations for the management of lipid disorders in those with the metabolic syndrome have been described in recent national guidelines. The recommendations emphasize lifestyle management (weight loss, physical activity, dietary fat restriction). However, the risk of cardiovascular disease (CVD) is increased in these individuals, making lipid treatment complex. Specific treatment targets and recommendations have not been fully clarified. Further data will be required before more specific recommendations regarding the diagnosis and treatment of lipid disorders in this syndrome can be developed. These issues will be addressed in detail in future revisions of the guideline as more definitive data become available.

Other management strategies for therapeutic lifestyle change (TLC) may include the following:

- Diet
- Aerobic exercise
- Weight management
- Smoking cessation
- Aspirin
- Sterol and stanol ester (Take Control® and/or Benecol® margarines and salad dressings), if taken as directed. Stanol ester is more effective and maintains efficacy longer.
- Fish oil (EPA-DHA)

Occlusive Vascular Disease (OVD)

OVD is defined as a diagnosis of carotid occlusive vascular disease, abdominal aortic aneurysm, or peripheral vascular disease. Patients with occlusive vascular disease are at increased risk for CHD, even without clinical symptoms of CHD. Physicians should help such patients decide whether aggressive lipid lowering is indicated. For patients with a history of stroke or cerebrovascular atherosclerosis, aggressive treatment with a statin-based regimen may be advisable.

Refer to the original guideline document for information on therapeutic lifestyle changes.

Evidence supporting these recommendations is of classes:

Diet: A, B, R
Aerobic Exercise: A, D, R
Weight Management: R
Smoking Cessation: C, R
Evaluate Alcohol Consumption: B, R
Fish oil (EPA-DHA): A, B, C, M, R
Aspirin: Primary Prevention: A, B, M, R
Sitostanol Ester Nutritional Supplement: A, C

7. Management and Treatment

The patient should receive dietary instruction through a class or individually from a registered dietitian or trained professional. Adjunctive measures (see Annotation #15, "Adjunctive Measures") should be reinforced. Secondary causes should be considered. (See Appendix C, "Identified Secondary Causes and Conditions Associated with Hyperlipidemia" in the original guideline document.) Lipid levels should be checked again in 6 weeks. Use of pharmacologic treatment is based on risk level and patient preference. Referral to a lipid clinic should be considered.

No primary prevention studies have addressed pharmacologic lipid treatment in persons at low risk for CHD, and there is no evidence to support drug treatment in this population. In particular, the incidence of CHD in men under 40 and premenopausal women is very low, and drug treatment in these groups is discouraged.

Primary prevention studies of pharmacologic lipid lowering have not shown a decrease in mortality, although most studies have shown about a 30 percent reduction in CHD events. Study populations have consisted predominately of middle-aged men, some with other risk factors. Similar benefit in higher-risk women can be assumed but has not been demonstrated.

The decision to begin and continue lipid-lowering medication should be made by the patient and the physician mutually.

Please refer to the table above, "Management," (Annotation Appendix B in the original guideline document) and Appendix D, "Drug Companion Document" in the original guideline document for additional information.

Please refer to Table 7 in the original guideline document for "Absolute Risk Reduction and Number Needed to Treat [NNT] with Pharmacologic Lipid Lowering."

The NNT can be presented to the patient as the number of people who would have to take medication for five years to prevent a non-fatal heart attack. (The major primary prevention studies have been 4 to 6 year studies). For example, if the NNT is 13, then 1 of 13 patients would benefit from treatment and 12 of 13 would not. Table 8 in the original guideline document lists primary prevention trials for prevention of CHD, including the type of therapy used and the NNT over 5 years for these trials.

Evidence supporting these recommendations is of classes: A, R

Treatment Options for Dyslipidemia

Reducing LDL-cholesterol (LDL-C) levels is the primary approach to lowering risk of CHD in both primary and secondary prevention. In some patients triglycerides may be elevated along with LDL-C so reducing triglycerides and increasing HDL-cholesterol (HDL-C) may also be desirable. Selection of drug therapy is dependent on several factors, including lipoprotein levels and percent reduction needed to attain goal; concurrent drug therapies that could increase the risk of side effects occurring with specific lipid lowering drugs;

presence of other medical disorders that may affect drug metabolism, increase risk of side effects, or be adversely affected by a specific lipid lowering drug.

Monotherapy

Statins are the drugs of choice for lowering LDL-cholesterol and aggressive treatment with statins should be pursued. Statins also have a modest effect on reducing triglycerides and increasing HDL-cholesterol. Several studies with clinical endpoints support use of statins in primary and secondary prevention.

If a patient is intolerant to a statin, clinicians are encouraged to have the patient try the other statins before ruling them all out. This is especially important in secondary prevention. In the Heart Protection Study, there was no significant difference between the simvastatin 40 mg and placebo groups in the number of patients with elevations of serum transaminases or unexplained muscle aches or weakness.

If patients are unable to take statins then bile acid sequestrants, niacin, fibric acids, and ezetimibe can be used.

Combination Therapy

Although combination therapy is not supported by outcome-based studies, some high-risk patients will require combination therapy. Most likely, these patients will have CHD. Using low doses of two complementary agents can often reduce LDL-cholesterol to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile acid sequestrant, with fewer side effects and possibly less cost. In very resistant cases, triple therapy may be needed.

In patients with mixed hyperlipidemia (increased LDL-cholesterol and triglycerides), the primary goal is decreasing LDL-cholesterol. A high triglyceride (200-499 mg/dL) with hypercholesterolemia signals a relatively high risk of CHD. These patients often have a low HDL-cholesterol. Combination of a cholesterol lowering drug with triglyceride lowering drug to achieve the non-HDL-cholesterol goal may be most warranted in patients with established coronary artery disease who are at very high risk of recurrent coronary events. Combining nicotinic acid with a statin is favorable for improving LDL-cholesterol, HDL-cholesterol, and triglycerides. Use of fibric acids leads to effective decrease in triglycerides and increased HDL-cholesterol, but effect on LDL-cholesterol is varied.

Please refer to Annotation Appendix D, "Drug Companion Document" in the original guideline document for information on drug efficacy, safety, risks, dosing, drug-food interactions, side effects, and monitoring.

8. Initiate Statin Therapy and Establish LDL Goals

Recent studies indicate that for patients with coronary artery disease or coronary artery disease equivalents, statin treatment significantly reduces mortality and major cardiovascular (CV) events regardless of baseline LDL levels. These data support the use of statins in such high-risk patients regardless of LDL level.

Specific statin and dose should be selected based on cost and amount of lipid lowering required. See Appendix D in the original guideline document, "Drug Companion Document" for additional information.

Thus, for care of patients with established CHD or CHD equivalent (which include occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, or diabetes), the use of statin therapy is recommended.

Bedtime or evening dose of statin is more effective (higher cholesterol synthesis).

To maximize absorption, lovastatin needs to be taken with food but lovastatin SR should be taken on an empty stomach.

Dosage adjustments should not be made more often than every 4 weeks after a fasting lipid panel.

Please consult manufacturer's product label insert, Physicians' Desk Reference (PDR), etc., for full prescribing information.

Patients Unable to Use Statin Therapy

If patients are intolerant to a statin, clinicians are encouraged to have the patient try the other statins in reduced doses before ruling out all statins. If patients are unable to take a statin, then bile-acid sequestrants, niacin, fibric acids, and ezetimibe are available.

Refer to the original guideline document for details on safety considerations in prescribing statins in primary care settings.

Evidence supporting this recommendation is of classes: A, R

9. LDL Goal Met?

Patients with CHD have an LDL goal less than 70 mg/dL. A recent trial provides evidence that intensive statin therapy to reduce LDL-cholesterol levels below 100 mg/dL showed substantial clinical benefit in patients with stable coronary artery disease (CAD).

If lipid goals are not met, it is important to intensify therapy until goals are reached. Lipid treatment is intensified within four months of an abnormal LDL value less than 20% of the time. This problem, referred to as "clinical inertia," is a major obstacle to improved lipid management.

Clinical inertia is defined as failure to intensify therapy at an office visit when the patient is above their evidence-based goal. Studies at Health Partners Research Foundation (HPRF) suggest that in high-risk patients such as those with diabetes or heart disease, clinical inertia may be found at over half the office visits.

Organized efforts to use decision support tools with or without electronic medical records may help reduce the problem of clinical inertia.

Evidence supporting this recommendation is of classes: A, R

10. Address Adherence

Suggested ways to improve adherence include asking about compliance in a non-threatening way at each visit; simplification of the drug regimen (frequency and complexity); reminder systems; drug-count devices; pill minders; involvement of family or friends; a health care team approach including nurses, dietitians, pharmacists and educators in addition to physicians; written instructions; and educating the patient about the medications including potential adverse effects, importance of therapy, realistic goals, necessity of life long treatment, and importance of continued attention to non-pharmacologic therapy (i.e., diet, exercise).

Additionally, the doctor-patient relationship can play a key role in improving compliance, in part through the physician's efforts to understand the patient's perspective on compliance.

- Assess the patient's knowledge of his/her medication and medical condition.
- Assess the patient's medication administration process.
- Assess the patient's barriers to adherence.

To view sample assessment questions, refer to the original guideline document.

For more information on adherence please refer to Appendix E, "National Cholesterol Education Program (NCEP) Recommendations on Strategies to Improve Adherence" in the original guideline document.

Evidence supporting this recommendation is of class: R

11. HDL Equal to or Greater than 40 and Triglycerides less than 200?

If the triglyceride level exceeds 400 mg/dL, the LDL-cholesterol level cannot be calculated according to the Friedewald formula. In such cases, a direct measurement of LDL-cholesterol, where available, can be used.

Non-HDL cholesterol becomes a secondary target when triglycerides are 200 to 499. The non-HDL target is 30 mg/dL higher than the LDL target. Non-HDL cholesterol is calculated by the formula non-HDL cholesterol = T cholesterol - HDL cholesterol.

Evidence supporting this recommendation is of classes: B, C, D

12. Laboratory Monitoring in 3-12 Months

Obtain a fasting lipid panel or lipid panel with direct LDL and transaminase as indicated (or see drug insert or drug companion).

Refer to Annotation Appendix D, "Drug Companion Document" in the original guideline document.

Evidence supporting this recommendation is of class: R

13. Health Maintenance

Health maintenance includes periodic monitoring, risk factor modification, and reinforcement of adjunctive measures (see Annotation #15, "Adjunctive Measures").

14. Evaluation and Management

Patients with primarily triglyceride elevation and normal or moderately elevated cholesterol are candidates for treatment if there is evidence of cholesterol rich very low- density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) particles, typically found in patients with triglyceride levels between 200-499 mg/dL and occasionally between 500-1000 mg/dL. If triglycerides are greater than 500, triglyceride lowering drugs become first-line therapy. The clinician may wish to consider the use of statin therapy. This is especially true if there is a strong family history of CHD and dyslipidemia, such as familial combined hyperlipidemia, or if the patient has evidence of atherosclerotic disease. Treatment can also be supported in diabetics with or without low HDL-cholesterol.

Patients with very high triglycerides (greater than 1000 mg/dL) are at increased risk of hepatomegaly, splenomegaly, hepatic steatosis and pancreatitis and are candidates for dietary and drug therapy. Patients with fasting triglycerides less than 1000 mg/dL are at less immediate risk of pancreatitis. After ruling out or controlling for secondary causes (e.g., diabetes mellitus, hypothyroidism, chronic renal failure, alcohol abuse, hormone replacement therapy and/or oral contraceptives), the National Institutes of Health recommend dietary measures for initial management of borderline and high triglycerides (please see Appendix C, "Identified Secondary Causes and Conditions Associated with Hyperlipidemia" for additional secondary causes). If dietary and lifestyle modification (weight reduction if needed, decrease in alcohol, increase physical activity, smoking cessation) does not lower triglycerides to desired level then drug therapy is indicated. (See Appendix D, "Drug Companion Document" and Appendix B, "Management." in the original guideline document.)

Uncontrolled glucose levels in patients with diabetes mellitus contribute to hypertriglyceridemia. Glucose levels in patients with diabetes should be under control to bring triglyceride levels under control.

When triglycerides are over 400 mg/dL, the LDL-cholesterol cannot be calculated and a direct measure of LDL, where available, is preferred. Although the LDL-cholesterol can be calculated when the triglycerides are moderately elevated (200-400 mg/dL), keep in mind that the LDL-cholesterol may be underestimated due to the Friedenwald equation.

LDL-cholesterol = Total cholesterol - HDL-cholesterol - (triglyceride divided by 5)

Evidence supporting this recommendation is of classes: A, R

15. Adjunctive Measures

Evidence suggests that adults with elevated lipid levels should follow the therapeutic lifestyle change or other equivalent diet. Nutritional assessment and evaluation should be carried out by a registered dietitian whenever possible. Please refer to Annotations #3-6, "Lifestyle Modification/Drug Therapy/Adjunctive Measures" for additional information.

16. Follow-Up

Coronary risk status and a lipid profile should be obtained at least annually.

Evidence supporting this recommendation is of class: R

Definitions:

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

CLINICAL ALGORITHM(S)

A detailed and annotated clinical algorithm is provided in the original guideline document for Lipid Management in Adults.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is classified for selected recommendations (see "Major Recommendations").

In addition, key conclusions contained in the Work Group's algorithm are supported by a grading worksheet that summarizes the important studies pertaining to the conclusion. The type and quality of the evidence supporting these key recommendations (i.e., choice among alternative therapeutic approaches) is graded for each study.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate management of lipids in adults
- Increased percentage of patients whose 10-year risk is greater than 20% or with known coronary heart disease (CHD) or CHD equivalent, who achieved low-density lipoprotein (LDL) treatment goals
- Improved percentage of patients with or without known CHD or CHD equivalent, with lipid disorders who meet their treatment goal
- Increased adherence with adjunctive treatment of patients with CHD or CHD equivalent through education
- Improved percentage of patients on lipid lowering medication who receive regular follow-up care for lipid disorder
- Increased percent of patients on lipid lowering therapy who remain on therapy

POTENTIAL HARMS

Potential Side Effects of Drugs

- Statins. Mild gastrointestinal (GI) complaints, headache, and insomnia may occur. Myopathy is rare with monotherapy (0.1%) and appears to be dose dependent; risk is increased with combination therapy. Hepatotoxicity appears to be dose dependent with occurrence estimated at 0.1 to 2.3%.
- Bile acid sequestrants. Not absorbed, so limited to GI tract. Constipation is most common with cholestyramine and colestipol. Bloating and belching also occur.
- Nicotinic acid. Side effects include flushing, transient pruritis, acanthosis nigricans, GI upset, increased uric acid, increased serum glucose, and hepatotoxicity.
- Fibric Acids. GI side effects are most common: dyspepsia, abdominal pain, diarrhea, and skin reaction. Rarely anemia, leukopenia, gallstones, atrial fibrillation, and myopathy may occur.
- Combination of nicotinic acid with a statin. An increased incidence of severe myopathy has been reported when a statin was combined with nicotinic acid or fibric acids. (In general, these combinations need not be avoided but careful patient selection, monitoring, and patient education are required.)

- Ezetimibe. Abdominal pain, diarrhea, sinusitis, arthralgia, and back pain were all reported in >3% of patients, but similar to placebo.
- Ethyl esters of omega-3 fatty acids; fish oil. Serious adverse effects include angina pectoris (1.3%). Common adverse effects include rash (1.8%), burping (4.9%), dyspepsia (3.1%), taste sense altered (2.7%), back pain (2.2%), and neurological pain (1.8%). Other adverse effects include infectious disease (4.4%), and influenza (3.5%)

Please refer to Annotation Appendix D, "Drug Companion Document," in the original guideline document for further information on safety concerns when using drug therapy.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Statins: Absolute contraindications include active liver disease, pregnancy, and lactation. Relative contraindications include alcohol abuse and primary biliary cirrhosis.
- Bile Acid Sequestrants: Absolute contraindications include complete biliary obstruction, bowel obstruction, triglycerides >400 mg/dL, and familial dysbetalipoproteinemia. Relative contraindications include triglycerides >200 mg/dL and patient on warfarin.
- Nicotinic acid: Absolute contraindications include active liver disease, active peptic ulcer, pregnancy/lactation, arterial hemorrhage, alcohol abuse, and severe gout. Relative contraindications include history of gout, high dose in type 2 diabetes mellitus (DM) or glucose intolerance, and renal dysfunction.
- Fibric acids: Absolute contraindications include severe hepatic impairment, and severe renal impairment. Relative contraindications include patients on warfarin.
- Combination of nicotinic acid with a statin. These combinations should generally be avoided in patients with acute or serious chronic illness (especially chronic renal disease), patients undergoing surgery or in patients who are already receiving cyclosporine, macrolide antibiotics, nefazodone, azole antifungal agents, or protease inhibitors.
- Combination of a statin and a fibrate. These combinations should be avoided in patients with impaired liver or renal function, patients on cyclosporine or tacrolimus therapy, long-term macrolide antibiotic therapy or azole antifungal therapy, patients of advanced age (greater than 70 years), and patients with skeletal muscle conditions.
- Ezetimibe: Absolute contraindications include use with statin in patients with active liver disease or unexplained persistent serum transaminase elevations. Relative contraindications include pregnancy, breast-feeding, moderate to severe hepatic insufficiency, and use with fibrates until studied in humans.
- Ethyl esters of omega-3 fatty acids; fish oil: Absolute contraindications include hypersensitivity to omega-3-acid ethyl esters or any component of the formulation. Relative contraindications include pregnancy and breast feeding.
- Aspirin should be avoided in patients with clinical history of bleeding diathesis, active ulcer disease or aspirin allergy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.
- This medical guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients are urged to consult a health care professional regarding their own situation and any specific medical questions they may have.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Once a guideline is approved for general implementation, a medical group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they may form an action group.

In the action group, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment, and tobacco cessation.

Detailed measurement strategies are presented in the original guideline document to help close the gap between clinical practice and the guideline recommendations. Summaries of the measures are provided in the National Quality Measures Clearinghouse (NQMC).

IMPLEMENTATION TOOLS

Clinical Algorithm
Patient Resources
Pocket Guide/Reference Cards
Quality Measures

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

RELATED NQMC MEASURES

- Lipid management in adults: percentage of patients with diagnosed coronary heart disease (CHD) or CHD equivalent who have had a diet evaluation.
- Lipid management in adults: percentage of patients on a lipid lowering medication who have a fasting lipid panel every three to twelve months.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Lipid management in adults. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2006 Jun. 76 p. [128 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1997 Oct (revised 2006 Jun)

GUIDELINE DEVELOPER(S)

Institute for Clinical Systems Improvement - Private Nonprofit Organization

GUIDELINE DEVELOPER COMMENT

Organizations participating in the Institute for Clinical Systems Improvement (ICSI): Affiliated Community Medical Centers, Allina Medical Clinic, Altru Health System, Aspen Medical Group, Avera Health, CentraCare, Columbia Park Medical Group, Community-University Health Care Center, Dakota Clinic, ENT Specialty Care, Fairview Health Services, Family HealthServices Minnesota, Family Practice Medical Center, Gateway Family Health Clinic, Gillette Children's Specialty Healthcare, Grand Itasca Clinic and Hospital, HealthEast Care System, HealthPartners Central Minnesota Clinics, HealthPartners Medical Group and Clinics, Hutchinson Area Health Care, Hutchinson Medical Center, Lakeview Clinic, Mayo Clinic, Mercy Hospital and Health Care Center, MeritCare, Mille Lacs Health

System, Minnesota Gastroenterology, Montevideo Clinic, North Clinic, North Memorial Care System, North Suburban Family Physicians, Northwest Family Physicians, Olmsted Medical Center, Park Nicollet Health Services, Pilot City Health Center, Quello Clinic, Ridgeview Medical Center, River Falls Medical Clinic, Saint Mary's/Duluth Clinic Health System, St. Paul Heart Clinic, Sioux Valley Hospitals and Health System, Southside Community Health Services, Stillwater Medical Group, SuperiorHealth Medical Group, University of Minnesota Physicians, Winona Clinic, Ltd., Winona Health

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GUIDELINE COMMITTEE

Cardiovascular Steering Committee

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

In the interest of full disclosure, Institute for Clinical Systems Improvement (ICSI) has adopted a policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. The reader should not assume that these financial interests will have an adverse impact on the content of the guideline, but they are noted here to fully inform readers. Readers of the guideline may assume that only work group members listed below have potential conflicts of interest to disclose.

Phillip M. Kofron, MD has received honoraria and expense reimbursement from Kos and Pfizer for speaker training. He has a speaker consulting agreement with

Pfizer but he has not made presentations or received speaker fees from Kos or Pfizer to date.

Stephen Kopecky, MD has done research for Endomatrix, Atherogenics, and Bristol Myers Squibb. He has also done consulting with Paringenix, Glaxo Smith Kline, Fibrex, and BioPhysical 250.

Thomas E. Kottke, MD has consulted with ASTRA-Zeneca.

No other work group members have potential conflicts of interest to disclose.

ICSI's conflict of interest policy and procedures are available for review on ICSI's website at www.icsi.org.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Lipid management in adults. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2005 Jun. 82 p.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Lipid management in adults. Executive summary. Bloomington (MN): Institute for Clinical Systems Improvement, 2006 Jun. 1 p. Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.
- ICSI pocket guidelines. April 2006 edition. Bloomington (MN): Institute for Clinical Systems Improvement, 2006. 298 p.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

PATIENT RESOURCES

The following is available:

- Lipid management in adults. Bloomington (MN): Institute for Clinical Systems Improvement, 2006 Jun.

Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI on July 10, 2000. The information was verified by the guideline developer on April 25, 2001. The summary was subsequently updated on August 17, 2001 following the withdrawal of the drug "Baycol (Cerivastatin)." The information was updated by ECRI on December 24, 2002. The information was verified by the guideline developer on January 23, 2003. The information was updated by ECRI on April 16, 2004, June 15, 2005, August 16, 2005, and on August 1, 2006.

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